

**REMARKS****I. Status of the Application**

Claims 1 through 36 are pending in the application. Claims 4, 7-10, 16, 18, 22, 23, 26, 27 and 29-36 are withdrawn from consideration. Claims 1, 2, 5, 11 and 12 are allowed. Claims 3, 6, 13-15, 17, 19-21, 24, 25 and 28 stand rejected under 35 U.S.C. §112, first and/or second paragraphs.

**II. Patentability Arguments****A. The rejection under 35 U.S.C. §112, 1<sup>st</sup> paragraph**

Claims 3, 14, 17 and 19 were rejected under 35 USC 112, first paragraph. According to the examiner, "the specification, while being enabling for a polynucleotide [SEQ ID NO: 12], encoding a yeast phenylalanine ammonia lyase (PAL) of SEQ ID NO: 13, vector, host cell and method of making the polypeptide recombinantly, does not reasonably provide enablement for any polynucleotide encoding PAL, wherein said PAL is at least 90% identical to SEQ ID NO: 13 or any polynucleotide which is at least 80%, 90% or 95% identical to SEQ ID NO: 12 (nucleotides 37-2196)." [Office Action, p. 3] The applicants respectfully disagree.

To be enabling as required by 35 U.S.C. §112, first paragraph, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. See *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Looking first at the subject matter of claims 14, 17 and 19, the examiner states these claims encompass all modifications of DNA of SEQ ID NO: 12 by 5% to 20%. This statement is only partially true; the examiner fails to state that all DNA within the scope of these claims must also encode a polypeptide having PAL activity. DNAs within the scope of the claims therefore represents a specific subset of all such modified DNAs.

In one aspect, the worker of ordinary skill in the art could readily prepare an enormous number of DNAs within the scope of each these claims based solely on degeneracy of the genetic code. For example, substituting each codon for serine with another serine codon alone would results in significantly different DNAs<sup>1</sup>, but each would still encode the

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<sup>1</sup> The serine codons are TCT, TCC, TCG, TCA, AGT, and AGC.

same biologically active PAL set out in SEQ ID NO: 13. Making and using such DNAs would require nothing more than routine experimentation.

In another aspect, DNAs within the scope of these claims would encode biologically active PAL polypeptides which differ in primary structure from that set out in SEQ ID NO: 13. In this instance, the subject matter of claim 3 joins the group. Whether making and using the invention would have required undue experimentation, and thus whether the disclosure is enabling, is a legal conclusion based upon several underlying factual inquiries, including: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. See *Enzo Biochem., Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1370-71 (Fed. Cir. 1999); *In re Wands*, 858 F.2d. 731, 735 (Fed. Cir. 1988). All of the *Wands* factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 U.S.P.Q.2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors “are illustrative, not mandatory. What is relevant depends on the facts.”).

Initially, it is submitted without proof that the relative skill of those in the art of recombinant enzymes is high. [*Wands* factor 6 above] If the examiner has reason to disagree with this position, the applicants respectfully request this position be explained.

As stated above, the breadth of the claims embraces all polynucleotides at least 80%, at least 90%, or at least 95% identical to the polynucleotide set out in SEQ ID NO: 12 and which encode a biologically active PAL, or polynucleotides which encode a biologically active yeast PAL which is at least 90% identical to the amino acid sequence set out in SEQ ID NO: 13. [*Wands* factors 4 and 8]

Looking next at the amount of guidance provided in the specification [*Wands* factor 2], the specification is replete with specific modifications which would fall within the scope of the claims, and how these modifications can be made. For example, at page, 12, beginning at line 8, deletion variants are described such as those: (i) comprising deletion of one, two, three, four, five or six residues at the amino and/or carboxy terminal ends [lines 13-14]; and (ii) carboxy terminal truncates also including additional amino terminal amino acid residues [lines 17-18]. The specification teaches that preparation of deletion fragment is well known in

the art, and again, if the examiner has reason to dispute this statement, evidence to the same is respectfully requested.

Likewise, at page 12, beginning at line 22, the specification describes in extensive detail preparation of substitution variants, and in particular conservative substitution variants. Exemplary conservative substitutions, those which are of strong and weak similarity, are set out in Table 1 at page 14. Still other substitution variants are described, beginning at page 12, line 29 and extending to the next page, wherein one amino acid is replaced with another giving consideration to size, shape, polarity, charge, hydrogen-binding capacity, solubility, chemical reactivity, hydrophobicity, hydrophilicity or amphipathic character of both the native residue and the desired amino acid to replace the native residue. Examples of similarly grouped amino acids are set out at page 13, beginning at line 10.

The specification also describes insertion variants, beginning at page 15, line 19, wherein additional amino acid residues are provided at either or both termini of the protein sequence, or alternatively, added within the native protein sequence. Fusion proteins are exemplified at page 15, line 25 and include the native PAL primary structure covalently modified to include immunogenic polypeptides, immunoglobulin sequences, marker proteins, amino acid sequences that facilitate purification, signal sequences, secretion sequences, sequences derived from certain expression systems.

As discussed above, preparation of polypeptide fragments are routine in the art. Likewise, preparation of insertion variants require nothing more than routine recombinant DNA technology, also routine in the art. Methods for preparation of other function derivatives are also well known in the art. For example, the specification teaches, beginning at page 18, line 7, *in vitro* synthesis, mutagenesis of DNA [line 14], and non-specific mutagenesis. Site specific mutagenesis is specifically exemplified beginning at page 18, line 30, known in the art to be carried out using common laboratory manuals or commercially available kits.

More importantly, the specification teaches that the worker of ordinary skill can be guided by changes known or made in PAL proteins from other species [p. 19, beginning at line 11]. Comparison of this nature is described in Example 3. This disclosure is significant because it teaches that the skilled worker is not operating in a complete void when it comes to modifying PAL enzymes. [This fact, and the statements of what was known in the art address *Wands* factor 5 above.]

While the specification admits that it is difficult to predict beforehand effects of certain changes in the primary structure of the PAL enzyme [*Wands* fact 7], the effect is evaluated by routine screening assays. An exemplary screening assay is disclosed in detail in example 4, page 66. Moreover, when the worker of ordinary skill compares the claimed PAL amino acid sequence to those sequences known in the art (as discussed immediately above), conserved regions become readily apparent, as well as potential substitutions which improve, or at least weakly attenuate, biological activity, making the effect of specific variations more predictable. [Addressing *Wands* factors 2 and 7 above]

Finally, the quantity of experimentation required to make certain variant will differ depending on the type of variant desired. For example, insertion variants wherein one or both termini are modified, and deletion variants wherein residues are removed from one or both termini, would require minimal experimentation. Internal insertion variants, deletion variant and substitution variants would reasonably be expected to require additional experimentation, if only to insure that the desired change in the encoding polynucleotide has been effected. Still, even this additional step is nothing more than routine. Even if one were to assert that making and using every embodiment of the claimed invention would require a tremendous amount of experimentation, the applicants point out this assertion cannot alone support an asserted lack of enablement.

A patent specification complies with the statute even if a “reasonable” amount of routine experimentation is required in order to practice a claimed invention, but such experimentation must not be “undue.” *See, e.g., In re Wands*, 858 F.2d at 736-37, 8 U.S.P.Q.2d at 1404 (“experimentation needed to practice the invention must not be undue experimentation. The key word is ‘undue,’ not ‘experimentation.’”) (footnotes, citations, and internal quotation marks omitted); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986) (enablement “is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly excessive.”). Such “routine” experimentation does not constitute undue experimentation:

The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired

embodiment of the claimed invention. *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564, 37 U.S.P.Q.2d 1618, 1623 (Fed. Cir. 1996) (quotation and citation omitted).

In view of all other *Wands* factors discussed above and in particular, the detailed guidance provided in the specification, and general knowledge in the art, the applicants submit that making and using the full scope of the claimed invention would be nothing more than routine and not undue experimentation. Accordingly, the applicants submit that the specification is enabling for the full scope of the subject matter of claims 3, 14, 17 and 19, and that the rejection of these claims under 35 U.S.C. §112, first paragraph may properly be withdrawn.

**B. The rejection under 35 U.S.C. §112, 2<sup>nd</sup> paragraph**

The examiner also rejected claims 6, 13 through 15 and 19 under 35 USC 112, second paragraph for various reasons, each of which is discussed below with regard to the specific claims.

Claims 6, 13 through 15 and 19 were rejected for reciting the term "residues" in the context of claimed polynucleotides. Amendment to the claims made herein removes the term "residues" and replaces it with the appropriate term, "nucleotides," thereby obviating the rejection.

Claim 6 was also rejected for reciting the abbreviation "T" with reference to specific nucleotides in sequence which the examiner asserted was not accepted. The applicants point to 37 CFR 1.822(b) which sets forth codes for nucleotide characters wherein each code letter recited in claim 6 is defined. Therein, "T" is defined to mean "thymine" The applicants therefore submit that the abbreviation would be understood in the art and that the rejection may be withdrawn.

Claim 20, 21, 24, 25 and 28 were rejected for reciting "A construct" which the examiner asserted to be unclear. The applicants respectfully disagree.

"[C]laims are not interpreted in a vacuum, but are part of, and are read in light of, the specification." *SciMed Life Systems, Inc. v. Advanced Cardiovascular Systems, Inc.*, 242 F.3d 1337,1341(Fed. Cir. 2001); *see Teleflex, Inc. v. Ficosa North America Corp.*, 299 F.3d 1313, 1325 (Fed. Cir. 2002)("The words used in the claims are interpreted in light of the

intrinsic evidence of record, including the written description, the drawings, and the prosecution history, if in evidence. The intrinsic evidence may provide context and clarification about the meaning of claim terms. Such intrinsic evidence is the most significant source of the legally operative meaning of disputed claim language.")(internal quotes and citations omitted) The applicants point to the specification at page 30, beginning at line 28, which provides an unambiguous definition of the term "construct."

A "construct" is any form of molecule in which a polypeptide sequence according to the invention or its encoding polynucleotide sequence is joined to or forms part of a larger molecule.

The applicants submit that this definition is unambiguous. Accordingly the rejection of claims 20 and 24, and claims that depend therefrom, may be withdrawn.

#### SUMMARY

In view of the foregoing remarks, the applicants submit that the rejected claims are now in condition for allowance and respectfully request notification of the same.

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Respectfully submitted,

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